Claims 1, 13-20, 23 and 29 were rejected under 35 U.S.C. 112, first paragraph.

At page 2 of the Advisory Action it is acknowledged that the application is enabling for a humanized monoclonal antibody which binds to Shiga toxin 1. New claim 30 and others call for such an antibody.

Moreover, as the specification makes clear, practice of the invention is not limited to a particular humanized monoclonal antibody or to a specific Shiga toxin.

With respect to the Shiga toxin, Applicants' disclosure teaches a variety of such toxins, collectively referred to as "Stx", that encompass a family of bacterial proteins produced by EHEC and *Shigella dysenteriae*. See eg., pg. 2, last full paragraph (disclosing a variety of Shiga toxins); pgs. 2-3, bridging paragraph and first full paragraph on pg. 3, (describing additional Shiga toxins and variants thereof). The specification also discloses immunological relatedness ("cross-reactivity") between the Shiga toxins eg., at pgs. 3-4, bridging paragraph. Additional illustrations of acceptable Stx are disclosed throughout the present application. See pgs. 2-4 of the application and references cited therein.

In particular, methods of preparing and using Stx-1 and Stx-2 toxin are described by Applicants such as at pages 27-32 (Examples 7-8).

With respect to humanized monoclonal antibodies, Applicants' disclosure provides for several of them.

For example, see pages 11-18 (Examples 1-3) describing production of the H13C4 antibody. See also Examples 4-7 on pages. 19-28 disclosing how to make the H11E10 antibody. Antibodies having particular nucleic acid and amino acid structures are shown in

Figures 3 and 6, for instance. Moreover, disclosure relating to preferred complimentarity determining regions (CDRs) and methods for manipulating same to achieve humanization is provided throughout the application including Figure 3 and the examples section. Antibodies that have the same binding activity as at least two well characterized murine monoclonal antibodies are also disclosed. Preferred antibodies include those which have modifications that do not appreciably diminish binding. See pg. 9. Pages 7-8 under "Detailed Description of the Invention" provide for additional humanized monoclonal antibodies that bind such Shiga toxin proteins.

Accepted methods for detecting and quantifying Stx binding are taught for example in the Examples section.

For example, Applicants' disclosure teaches immunological assays for identifying and testing suitable antibodies *in vitro*. See Example 7 (disclosing preferred Vero cell and antisera neutralization assays). A passive immunization protocol for testing such antibodies *in vivo* has also been disclosed for instance, in Example 8, pages 29-32 of the application.

The instant rejection appears to attempt to limit Applicants' claims to specific disclosed embodiments. That is not proper under the law. Thus in *In re Anderson*, the CCPA reversed a rejection under Section 112, first paragraph and noted in particular (176 USPQ at 333):

> What the Patent Office is here apparently attempting is to limit all claims to the specific examples, notwithstanding the clear disclosure of a broader invention. **This it may not do**.... There is no doubt that a patentee's invention may be broader than the particular embodiment shown in his specification. A patentee is not only entitled to narrow claims directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. (emphasis added).

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 1, 2, 13-20, 23 and 29 were 35 U.S.C. 103 over Spiers (Can. J. Microbio.) or O'Brien et al. (U.S. Patent 5,747,272) in view of Shitara et al. (U.S. Patent 5,866,692). The rejection is traversed.

The cited documents fail to provide any amino acid or nucleic acid sequence information relating to a humanized an anti-shiga toxin monoclonal antibody.

The rejections set forth in the Advisory Action also are contradictory. Under Section 112, the disclosure of how to make and use the claimed invention is questioned, and under the instant Section 103, it is contended that the claimed subject matter would have been obvious.

As the rejection is understood, the position is taken that it would be obvious to synthesize and express a chimeric antibody that binds to Shiga-like toxin type 2 and that it would be obvious to humanize that antibody. The position is believed to arise from Shitara's report of a DNA-based method for humanizing antibodies (see for example, cols. 3-4 of the patent). Embedded in the PTO's argument is the contention that it would be obvious to make DNA encoding Applicants' antibody; specifically to isolate, sequence and analyze that DNA, and to humanize antibody encoding DNA sequence along lines of Shitara as cited. Respectfully, the position is at odds with decisions of the Federal Circuit and current USPTO examination practice.

The Federal Circuit has made it abundantly clear that not even a prior art disclosure of a protein sequence renders a particular DNA obvious. See eg., *In re Deuel*, 51 F.3d 1552, 1558-59, (Fed. Cir. 1995). More is needed. However, in the instant case, the PTO has not even reached the threshold addressed by *Duel.* That is, it has not cited any sequence of any humanized anti-shiga toxin monoclonal antibody in formulating the rejection. Nonetheless, the

Office urges that obtaining Applicants' antibody would be obvious in the face of no sequence information. Respectfully, the position is completely without merit under the case law and should be withdrawn. Not even a partial protein sequence of any humanized anti-shiga toxin monoclonal antibody has been cited against Applicants. Even assuming, *arguendo*, that such minimal information was cited, the instant obviousness rejection would still fail in view of applicable case law. See *In re Deuel,* Id. MPEP § 2144.09. See also See *In re Bell* 51 F.3d 1552 (Fed. Cir. 1995).

In contrast, it is Applicants who disclosed how to humanize an anti-Stx 1 antibody (13C4), specifically by showing how to identify and clone a 13C4 antibody variable cDNA; how to construct and express vectors encoding appropriate antibody heavy and light chains including suitable subcloning manipulations. See Examples 1-2 on pgs. 11-17. Stable production of a recombinant mouse/chimera 13C4 antibody was also shown on pgs. 18-19.

Importantly, Applicants sequenced the DNA of EHEC anti-Stx2 antibody 11E10 to assist the disclosed antibody humanization process. See the disclosure at pgs. 19-23. That sequence information is provided in Figure 6 and was instrumental in identifying and manipulating certain CDR regions. Also importantly, the DNA sequence obtained by Applicants assisted efforts to make a variety of useful PCR primers. See eg., Figure 5.

None of the cited references, when taken alone or in combination, teaches or suggests how to make or manipulate the DNA information furnished by Applicants. There would be no motivation to make Applicants' humanized monoclonal antibodies in view of those references.

In view thereof, reconsideration and withdrawal of the rejection are requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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